REMARKS

Reconsideration is requested.

Claims 1-10 and 12 have been canceled, without prejudice.

Claims 19-22 have been added and find support throughout the specification. The details of claim 12 have been added to the above-amended claim 11.

Moreover, claim 11 has been amended to obviate the Section 112, second paragraph, rejection of claims 11-16 in that dermal fibroblasts are transduced ex-vivo according to the claimed invention. Reconsideration and withdrawal of the Section 112, second paragraph, rejection of claims 11-16 are requested.

The Section 102 rejection of claims 17-18 over Murry (1996, Journal of Clinical Investigation, Vol. 98 (10), 2209-2217), is obviated by the above amendments. Specifically, Murry fails to teach transient expression of a muscle lineage commitment gene in a genetically modified fibroblast which has been transduced with a therapeutic gene or a gene capable of correcting a gene defect. With regard to claim 21, and claims dependent therefrom, Murry fails to teach transient expression of a muscle lineage commitment gene in a genetically modified dermal fibroblast. The claims are submitted to be patentable over Murry. Reconsideration and withdrawal of the Section 102 rejection of claims 17 and 18 over Murry is requested.

The Section 103 rejection of claims 11 to 16, over WO 96/09373 (Watt et al.) in view of Choi (1990, PNAS, Vol. 87, 7988-7992) and Murry (1996, J. Clin. Invest., Vol. 98, No. 10, 2209-2217) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

Watt et al. describe a method of treatment of muscular disorders in a patient,

which comprises administering to or adjacent to the muscle cells of the patient immunologically compatible dermal fibroblast cells under conditions effective to convert the dermal fibroblast cells to myogenic cells. See, claim 1, page 23 of Watt. In the conditions described by Watt et al., myogenic conversion, i.e., the process by which a fibroblast becomes a myogenic cells and makes new muscle, is intended to occur spontaneously upon injection into the muscle of the patient. Spontaneous myogenic conversion however, occurs at a very low frequency, its outcome is unpredictable, and it is of no practical use as a therapeutic intervention. No therapy for muscular dystrophies has ever been known to have developed based on such a low-efficiency technology. Watt et al. do not teach how to increase the frequency of myogenic conversion of fibroblasts to a level that would make it practically usable in a clinical setting. As such, the method described by Watt et al. cannot be practiced by a person having ordinary skill in the art in order to cure or treat a muscle disorder.

The Examiner notes in Paper No. 11 on page 8, with regard to the applicants view of Watt, that (a) only claim 12 recites a rate of conversion and (b) Watt was not cited for teaching myoconversion of dermal fibroblasts but rather that dermal fibroblasts removed from a patent with a muscular disorder were transduced with a vector encoding dystrophin. The Examiner notes that the rates of myoconversion of fibroblasts by expression of myoD were supplied by Choi et al. and Murry et al. See, page 9 of Paper No. 11.

With regard to (a) above, claims 11 and 13-16 recite a conversion rate of greater than 40%.

With regard to (b) above, the applicants urge the Examiner to appreciate that the

fact that the spontaneous myoconversion of Watt was unpredictable and of low efficiency is relevant to the expectations of one or ordinary skill in the art – irrespective of whether the Examiner is relying on that fact. The teaching of Watt, as a whole, will be understood to teach an impractical method for making useful genetically modified dermal fibroblasts. The Examiner has not refuted that Watt teaches an inefficient and unpredictable method, as previously explained by the applicants and reiterated above.

The presently claimed invention provides a method of making fibroblasts which may be used as a source of muscle cells and the use of a *high-efficiency, non-integrating viral vector* to achieve transient expression of a muscle-determination gene, for example myoD, in an in vitro culture.

As noted above, the Examiner relies on Choi et al. to allegedly teach a rate of myoconversion of fibroblasts by expression of myoD.

Choi et al. do not teach or suggest the myoconversion of genetically modified dermal fibroblasts. Choi et al. teach, at best, "5% or less" conversion of dermal fibroblasts, as admitted by the Examiner. See, page 7 of Paper No. 11.

Choi et al. may describe that the expression of myoD into dermal fibroblasts induces their conversion into muscle cells. However, Choi et al. use an integrating retroviral vector, which implies the permanent acquisition of the gene by the transduced fibroblasts. Due to the combination of the low efficiency of gene transfer obtained with this type of vectors, and the anti-proliferate action of the permanently acquired myoD gene, the efficiency of myogenic conversion obtained by the method described by Choi et al. is in the range of 1 to 5% (page 798, right column, line 8). This efficiency is not significantly different from that obtained by the spontaneous conversion described by

Watt et al., and is again of no practical use.

Choi et al. therefore is deficient with regard to the claimed invention in not teaching or suggesting myoconversion of genetically modified dermal fibroblasts and in not teaching or suggesting a method of myogenically converting genetically modified fibroblasts at a rate of greater than 40%, as presently claimed.

The Examiner has criticized the applicants previous submission of similar remarks by noting that "this line of reasoning is not compelling in regards to applicant's claims 11, and 13-16, since the claims as written read on any rate of myoconversion in fibroblasts" (see, page 9 of Paper No. 11). Claims 11 and 13-16 recite a conversion rate of greater than 40%. The Examiner will now presumably find the above arguments relating to Choi et al. to be compelling.

The Examiner has separately "reminded" the applicants that "one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references." See, page 8 of Paper No. 11.

While the Examiner's reminder is noted with appreciation, the Examiner is urged to appreciate that the above and previously submitted remarks specifically point out that one of ordinary skill in the art reading both Watt and Choi would not have considered that Choi provided any improvement in the poor results of Watt, i.e., low efficiency myogenic conversion. Choi therefore would not have motivated one of ordinary skill in the art reading Watt and Choi in combination to make the presently claimed invention with any expectation of success.

With regard to Murry, the Examiner notes that the applicants previous arguments relating to the previously cited Murry (1995, FASEB, Vol. 9, No. 4, A883) and the lack of

a teaching of the frequency of myoconversion of cardiac fibroblasts therein are not relevant to the currently cited Murry (1996) "which teaches rates of myoconversion stemming from infection of fibroblasts with adenovirus encoding myoD." See, page 9 of Paper No. 11.

The Examiner has not however addressed the applicants previously noted deficiency of Murry (1995), which is also a deficiency of the presently cited Murry (1996). Specifically, Murry teaches the use of *cardiac* fibroblast as a source of cells for their specific application, i.e., improvement of the *heart muscle* function. Accordingly, the applicants submit that one of ordinary skill in the art would not have reasonably expected to combine the teachings of Murry, relating to cardiac fibroblasts with the dermal fibroblasts of Choi and/or Watt. In practical terms, the results of Murry et al do not predict or imply or suggest that the use of an adenoviral vector might improve the efficiency of myogenic conversion of *dermal* fibroblasts in culture for the specific purpose of *skeletal muscle* implantation.

More importantly, the Examiner has admitted on page 7 of Paper No. 11 that, at best, Murry provides a method of myogenic conversion of cardiac fibroblasts of no more than 14%. See, Figure 3B of Murry and accompanying text. This is compared with the "5% or less" taught by Choi et al. See, page 7 of Paper No. 11.

The Examiner has indicated that (i) the conversion rate of claim 12, now recited in claim 11, would have been inherently provided by the vector of Murry and that (ii) the reliance on inherency is not improper even though the rejection is based on Section 103 instead of Section 102. See, page 10 of Paper No. 11.

With regard to (i) above, the applicants urge the Examiner to appreciate that the

presently claimed invention, as recited in claims 11 and 13-16, require transient infection of genetically-modified dermal fibroblasts, as opposed to the stable infection of cardiac fibroblasts taught by Murry. The Examiner's focus on the vector alone is inappropriate as consideration of the whole of the cited art would not have led one of ordinary skill in the art to the whole of the presently claimed invention. The applicants are not claiming a use of the vector of Murry in the manner used by Murry on a substrate (i.e., cardiac fibroblasts) used by Murry. Rather, the applicants are claiming, in claims 11 and 13-16, a method for myogenic conversion of cells not described or suggest in Murry to produce cells not taught or suggest by Murry. The "structure recited in the reference" (see, page 10 of Paper No. 11), as a whole therefore is not "substantially identical to that of the claims" and the result (i.e., the rate of myogenic conversion) would not have been inherent from Murry.

With regard to the Examiner's reliance on In re Skoner, 186 USPQ 80 (CCPA 1975) (copy attached) and point (ii) above, the applicants note that Skoner was apparently using a process of brushing found in the cited art (i.e., Baer et al.) which Skoner asserted to be of a different extent. The Skoner court however found that the Examiner reasonably concluded that because Baer et al. was using "identical means (i.e., wire brushing) in an attempt to achieve identical results (i.e., improved adhesion)", the Examiner had established a *prima facie* case obviousness. See, 186 USPQ 82. The Skoner court went on to note that the rejection of Skoner's claims should of perhaps been founded on §102 instead of §103 as Baer et al. was a complete disclosure of Skoner's claimed invention.

In the present case, the applicants are not using, for example, identical means,

i.e., the presently claimed transient infection of transduced dermal fibroblasts versus Murry's stable infection of cardiac fibroblasts, in an attempt to achieve identical results (i.e., the myogenically converted genetically modified dermal fibroblasts of the present invention versus skeletal muscle in Murry). Accordingly, In re Skoner is not believed to support or justify the Examiner's reliance of Murry.

The applicants note the reminder in Skoner that evidence of unexpected beneficial results are evidence of unobviousness. See, 186 USPQ 82. The present Examiner has not commented on the applicants previous remarks relating to the unexpected beneficial results provided by the presently claimed invention.

Specifically, the presently claimed invention is based on an entirely new concept, which is not suggested by the cited art. The presently claimed invention achieves myogenic conversion of dermal fibroblasts by *transient expression of high levels* of a muscle-determination gene, in particular myoD, with an adenoviral vector or a vector with comparable characteristics. The presently claimed method allows *massive,* i.e. more than 50%, conversion of fibroblasts ex vivo, resulting from both high efficiency of gene delivery to the cultured fibroblasts (more than 95%) and high efficiency of gene expression obtained by the high number of gene copies introduced into the cells by the non-integrating vector. Furthermore, since no integration of the gene into the genome of the fibroblasts is required, the cells can be used immediately after exposure to the transiently infecting vector, without any further culture steps such as those described by Choi et al., which invariably result in reduction of cell viability and cell aging. The difference is substantial and not merely technical: in order to be useful for therapeutic purposes, the majority of the injected fibroblasts must be converted to a muscle fate

before, or upon, injection into the muscle tissue, and must engraft at high efficiency as they do under the conditions that the present applicants describe.

The fact that human fibroblast can be converted to muscle cells with such a high efficiency ex vivo was not obvious from the cited art. High efficiency was not considered by Watt et al. as a pre-requisite for the practical application of myogenic conversion. On the contrary, the applicants describe in both the present specification, and in a subsequent publication (Lattanzi et al., J. Clin. Invest. 101: 2119-2128 (attached)) that only high efficiency allows the practical use of converted dermal fibroblasts. The applicant therefore disagree with the Examiner's conclusion that an ordinarily skilled artisan would have had a reasonable expectation of success based on the combined knowledge provided by Choi et al, Murry et al. and Watt et al.

For these reasons, the applicants submit that the overall concept of transient, high-level expression of a muscle-determination genes described and presently claimed is patentable over the cited art.

Withdrawal of the Section 103 rejection is requested.

In view of the above, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Should the Examiner believe that an interview with the undersigned would facilitate allowance of this application, the Examiner is encouraged to contact the undersigned.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1632

In re Patent Application of

MAVILIO

Serial No. 09/674,853

Filed: November 7, 2000

Title: GENETICALLY-MODIFIED FIBROBLASTS AND THE USE THEREOF

OIPE JC15 OCT 17 2003 PATENT & TRADEMARK OFFICE

Atty Dkt. 1303-110 41
C# M#

Group Art Unit: 1632

Examiner: Wehbe

Date: October 17, 2003

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **11** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **3** minus highest number previously paid for **3** (at least 3) = 0 x $ 86.00	$	0.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	110.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**110.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☒ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	55.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Other: Copy of *In re Skoner*, 186 USPQ 80 (CCPA 1975), pgs. 80-83; Copy of publication (Lattanzi et al., Clin. Invest. 101: 2119-2128); Extension Petition; Extension Fee (1 Month - Small Entity)		**0.00**
TOTAL FEE ENCLOSED	$	**55.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of Atty Dkt. 1303-110
C# M#

MAVILIO Group Art Unit: 1632

Serial No. 09/674,853 Examiner: Wehbe

Filed: November 7, 2000 Date: October 17, 2003

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